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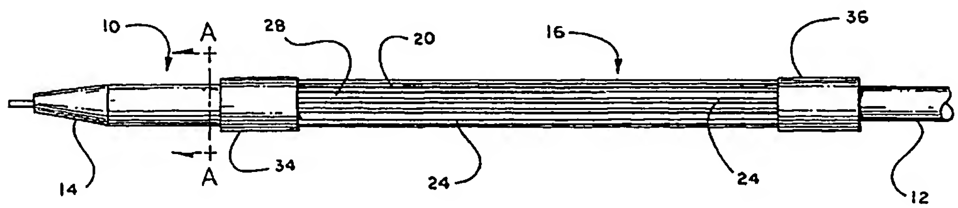


(57) Abstract

Use of anti-angiogenic agents to inhibit an undesireable response to vessel wall injury, including stent neointima, dialysis graft neointima, vascular graft induced neointima, and the treatment of benign hypertrophic scar formation as well as the treatment and passivation of unstable atherosclerotic plaques are provided. The invention provides for the use of catheter-based devices for enhancing the local delivery of anti-angiogenic agents into the endothelial tissues of blood vessels of the living body.

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# USE OF ANTI-ANGIOGENIC AGENTS FOR INHIBITING VESSEL WALL INJURY

## Field of the Invention

The present invention includes anti-angiogenic agents and their use in inhibiting the response to vessel wall injury, such as that caused by stent neointima, dialysis graft neointima, vascular graft induced neointima, and the treatment of benign hypertrophic scar formation, as well as the treatment and passivation of unstable atherosclerotic plaques.

## Background of the Invention

The response to tissue injury remains one of the major limitations of percutaneous angioplasty procedures and stent placement. The response of the vessel wall to the balloon barotrauma, stent placement, placement of a vascular graft (arterial, or arteriovenous graft e.g., dialysis graft) remains a significant limitation of these procedures. This response is a complex interaction of inflammation, smooth muscle cell migration, proliferation and myofibroblast transformation that occurs as soon as the barotrauma/trauma occurs and can in a varying number of patients, limit the procedures success.

Anti-angiogenic agents are typically administered through systemic therapies, such as by intramuscular or subcutaneous injection. In these treatments there is an immediate dilution effect greatly reducing the concentration of the agent to which the target tissues or cells are exposed. Also, medicines administered by these systems may be more vulnerable to processes such as metabolic degradation, inactivation by binding to plasma proteins or accelerated clearance from the body. These processes adversely affect the drug's concentration and residence time in the target tissues and reduce its therapeutic efficacy.

Most of the above modes of drug administration also expose non-target tissues, i.e. those that do not require treatment, to the action of the drugs, with the consequent risk of serious side effects. It is this risk towards non-target tissues that reduces a drug's efficacy by restricting systemic concentrations to a threshold level above which side effects would become unacceptable.

Angioplasty procedures generally involve the introduction of a small balloon catheter into the femoral artery in a patient's leg and, with the help of a guide wire, the catheter is passed by remote manipulation under fluoroscopy into the heart. The balloon can then be positioned in a region of a coronary artery that has become constricted due to atherosclerosis and by inflating and deflating the balloon several times the bore of the diseased artery is mechanically widened until a satisfactory blood flow through the vessel has been restored. If the artery is severely damaged by disease, and perhaps hardened by calcium deposition, this balloon inflation may also cause some degree of additional injury with local de-endothelialisation and exposure of underlying extracellular matrix components such as collagen and elastin. In a few patients excessive recruitment of platelets and fibrinogen can then result in an acute thrombotic occlusion. This is now less common, however, with the routine use of heparin and aspirin cover during the angioplasty procedure.

Generally, angioplasty procedures produce excellent results obviating the need for bypass surgery, but in about 30 - 40% of patients, an ostensibly successful initial dilatation of the artery may be followed by a renarrowing of the vessel (restenosis) some 3 to 9 months later. If this restenosis is severe, these patients may require a second angioplasty procedure, often with implantation of a stent to act as a scaffold in the vessel. In other cases arterial reconstruction under by-pass surgery, which is a higher risk procedure, may be required. With more than 800,000 PTCA procedures now performed world-wide annually, the socio-economic implication of this 30 - 40% restenosis rate has become a matter of serious concern to interventional cardiologists.

The pathophysiology of this late restenosis is complex, and involves a wide range of cellular and molecular responses, many of which are not yet fully understood. Although a number of putative targets for drug interference have been identified, more than 50 clinical trials (some large and multi-center) with a wide range of different drugs have failed to reveal a satisfactory pharmacotherapeutic approach to reducing the incidence of restenosis. One problem is that for some of the potentially useful drugs, it is not possible by systemic administration to get a therapeutically effective level of the drug in the vessel wall tissue without significantly affecting non-target tissues elsewhere.

Accordingly, what is needed are methods for delivering anti-angiogenic treatment agents to specific locations, including intracellular locations in a safe and effective manner. These methods would deliver the agents to an injured site in effective amounts without endangering normal tissues or cells and thus reduce or prevent the occurrence of undesirable side effects.

## Summary of the Invention

The present invention provides for the specific localized use of anti-angiogenic agents to prevent and inhibit an undesirable response to vessel wall injury, including stent neointima, dialysis graft neointima, vascular graft induced neointima, and the treatment of benign hypertrophic scar formation as well as the treatment and passivation of unstable atherosclerotic plaques.

The present invention provides the use of anti-angiogenic substances and their derivatives via local drug delivery devices/catheters or via stents and stent coatings and vascular grafts and graft coating technologies, for example. The invention also provides methods of administering anti-angiogenic agents in compositions that elute out regulated quantities of the anti-angiogenic compounds over time in a localized area.

In particular, one embodiment of the present invention relates to uses of catheter-based devices which provide an electrical driving force that can increase the rate of migration of drugs and other therapeutic agents out of a polymer matrix into body tissues and cells using iontophoresis only, electroporation only, or combined iontophoresis and electroporation. A preferable approach may be for electroporation to be applied to permeabilize the cells after pre-iontophoresis of the anti-angiogenic agent into the tissues. Preferably, the catheter is able to perform the two procedures sequentially without repositioning of the catheter. Even more preferably, the catheter is designed to maintain a high concentration of drug in the tissue extracellular spaces (e.g. by iontophoresis) such that the subsequent creation of transient pores in cell surface membranes by electroporation pulses results in greatly improved intracellular delivery of the treatment agent.

The present invention is particularly applicable to the local delivery of anti-angiogenic drugs during and after interventional cardiology procedures such as angioplasty and stent implantation.

Accordingly, it is an object of the present invention to provide methods for enhancing the local delivery of anti-angiogenic agents.

It is another object of the present invention to provide methods for the local delivery of angiogenic treatment agents into the wall tissues or cells of the living body.

It is another object of the present invention to provide methods for the localized treatment of undesirable angiogenesis such as restenosis and atherosclerosis.

It is another object of the present invention to provide methods to deliver treatment agents to specific tissues and cells without endangering non-targeted tissues and cells.

It is another object of the present invention to provide methods which use iontophoresis and/or electroporation to enhance the local delivery of treatment agents.

It is another object of the present invention to provide methods of enhancing anti-angiogenic drug delivery to blood vessel walls.

These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and the appended claims.

**Brief Description of the Drawings**

Figure 1 shows a catheter-based device for drug delivery according to its relaxed position.

Figure 2 shows a catheter-based device for drug delivery according to its expanded position of the present invention.

Figure 3 is a cross-sectional view taken along line a-a of the catheter-based device according to a first embodiment of the present invention.

Figure 4 is a cross-sectional view taken along line a-a of the catheter-based device according to a second embodiment of the present invention.

Figure 5(a) shows the electrode network of a PCB electrode according to a second embodiment of the present invention.

Figure 5(b) shows the base layers and the location of etched slots in a PCB electrode according to a second embodiment of the present invention.

Figure 5(c) shows a composite detailed diagram of the base with slots and the electrode network of a PCB electrode according to a second embodiment of the present invention.

Figure 6 shows a cross-sectional view of a preferred PCB electrode embodiment.

**Detailed Description of the Invention**

Neovascularisation, otherwise known as angiogenesis, appears to be a central component of the response to tissue injury. The present invention provides the use of anti-angiogenic substances and their derivatives via local drug delivery devices, such as catheters or stents and stent coatings and vascular graft coating technologies, that elute out regulated quantities of the anti-angiogenic compounds locally to the injured tissue. This therapeutic approach is aimed at reducing the angiogenesis that occurs locally at the site of injury, thus potentially reducing or preventing undesirable responses to injury, such as narrowing, renarrowing or restenosis of veins and arteries.

The present invention relates to the inhibition of undesirable angiogenesis with a consequent reduction in the delivery and release of $O_2$ and substrates of metabolism within the vessel wall and a reduction in the removal of the waste products of metabolism. The invention renders the microenvironment unfavorable for migration and proliferation

of smooth muscle cells, inflammatory cells and other cells involved in the undesirable response to injury.

According to the present invention, the anti-angiogenic compounds include, but are not limited to, AGM-1470 (TNP-470) or antagonists to one of its receptors MetAiP-2; growth factor antagonists or antibodies to growth factors (including VEGF or bFGF and the family of fibroblast growth factors); growth factor receptor antagonists or antibodies to growth factor receptors; inhibitors of metalloproteinases including TIMP, batimastat (BB-94), and marimastat; tyrosine kinase inhibitors including genistein and SU5416; integrin antagonists including antagonists alphaVbeta3/5 or antibodies to integrins; retinoids including retinoic acid or the synthetic retinoid fenretinide; steroids 11 α-epihydrocortisol, corteloxone, tetrahydrocortisone and 17 α-hydroxyprogesterone; protein kinase inhibitors including staurosporine and MDL 27032; vitamin D derivatives including 22-oxa-1 alpha, and 25-dihydroxyvitamin D3; arachidonic acid inhibitors including indomethacin and sulindac; tetracycline derivatives including minocycline; thalidomide derivatives; estradiols derivatives such as 2-methoxyestradiol; tumor necrosis factor-alpha; interferon-gamma-inducible protein 10 (IP-10); interleukin 1 and interleukin 12; interferon alpha, beta or gamma; Angiostatin® protein or plasminogen fragments; Endostatin™ protein or collagen fragments; proliferin-related protein; group B streptococcus toxin; CM1O1; CM; troponin I; squalamine; nitric oxide synthase inhibitors including L-NAME; thrombospondin; wortmannin; amiloride; spironolactone; ursodeoxycholic acid; bufalin; suramin; tecogalan sodium; linoleic acid; captopril; irsogladine; FR-1 18487; triterpene acids; castanospermine; leukemia inhibitory factor; lavendustin A; platelet factor-4; herbimycin A; diaminoantraquinone; taxol; aurintricarboxylic acid; DS-4152; pentosan polysulphite; radicicol; fragments of human prolactin; erbstatin; eponemycin; shark cartilage; protamine; Louisianin A, C and D; PAF antagonist WEB 2086; auranofin; ascorbic ethers; and sulfated polysaccharide D 4152, anti-keloid agents including TRANILAST. The present invention also includes lipophillic, and charged derivatives of anti-angiogenic compounds. The invention is intended to encompass the use of currently known anti-angiogenic agents, or their active derivatives or analogues, and those discovered in the future.

The amount of anti-angiogenic agent to be applied to injured vascular tissue is highly variable depending upon the type and efficacy of anti-angiogenic agent selected, the extent of the injury, the condition and responsiveness of the patient, the aggressiveness of the physician's regimen, and so forth. However, the determination of an angiogensis inhibiting effective amount of an anti-angiogenic agent in any particular circumstances would be within the routine skill of artesans in view of the present disclosure. By "injured" or "injury" in the context of vascular tissue is meant any veinous or arterial irregularity from normal healthy living tissue, which is marked by

angiogenic activity. For example, injured vascular tissue may be the result of biological disease, such as atherosclerosis, or due to interventional disruption, such as restenosis. By "local" administration is meant the delivery of an anti-angiogenic agent to the targeted vascular tissue such that an increased concentration of the anti-angiogenic agent is present at the targeted vascular tissue in comparison to other tissues.

In one embodiment of the present invention, the anti-angiogenic compounds are incorporated into polymers or co-polymers and are eluted out into the microenvironment for local biological activity. In addition, the anti-angiogenic compounds or their active derivatives or analogues can be incorporated into metallic or polymeric stents, stent coatings including, but not limited to, absorbable, biocompatible and non-absorbable polymers, endovascular grafts, endovascular graft coatings, paved stents, endoluminal paving with gels and hydrogels and polymeric stent sheaths. Furthermore, these compounds can be administered in a state associated with, incorporated in, or attached to the surface of microparticles, colloidal gold or liposomes to tissues at risk of excessive angiogenic response to injury.

In addition, the present invention includes treating at-risk groups of patients locally (e.g. endoluminally or topically) with active anti-angiogenic compound following evidence of an episode of atherosclerotic plaque instability. The treatments herein include local application of the compound, and repeated dosing, perhaps with a systemic therapy, including combinations of anti-angiogenic agents and other therapeutic agents.

The present invention includes the use of anti-angiogenic compounds and similar compounds and their derivatives for the treatment of the following classes of diseases including, but not limited to, atherosclerosis, cardiac transplant vasculopathy, coronary restenosis following coronary intervention including, but not limited to, balloon angioplasty, stent placement, rotablator, and other endoluminal procedures; carotid endarterectomy, stenting and angioplasty, peripheral artery and renal artery angioplasty and stent placement, dialysis graft stenosis (venous or arterial end), large and small bore graft anastomosis neointima, and the inclusion of these compounds in the matrix of the graft, unstable coronary plaques, e.g. those occurring in unstable angina, acute myocardial infarction, stroke (carotid plaque ulceration). Additionally the present invention includes the use of anti-angiogenic compounds either endoluminally, topically or systemically in conditions of benign hypertrophy or tissue including benign prostatic hypertrophy, ingrowth of benign liver tissue in to stents placed during the TIPS procedure, Keloid disease of the skin and other hypertrophic skin diseases including eczema and psoriasis.

In particular, the present invention relates to the use of anti-angiogenic agents in catheter-based devices which can provide an electrical driving force that can increase the rate of migration of drugs and other therapeutic agents out of a polymer matrix into body

tissues and cells using iontophoresis only, electroporation only, or combined iontophoresis and electroporation. A preferable approach may be for electroporation to be applied to permeabilize the cells after pre-iontophoresis of the agent into the tissues. Preferably, the catheter is able to perform the two procedures sequentially without repositioning of the catheter. Even more preferably, the catheter is designed to maintain a high concentration of drug in the tissue extracellular spaces (e.g. by iontophoresis) such that the subsequent creation of transient pores in cell surface membranes by electroporation pulses results in greatly improved intracellular delivery of the treatment agent. The invention provides methods of inhibiting angiogenesis by applying electrical driving forces to enhance local delivery of anti-angiogenic agents to injured tissues. The present invention is particularly applicable to the local delivery of drugs during interventional cardiology procedures such as angioplasty, stent implantation etc.

In particular, the present invention relates to the use of catheter-based devices which provide an electrical driving force that can increase the rate of migration of drugs and other therapeutic agents out of a polymer matrix into body tissues and cells using iontophoresis only, electroporation only, or combined iontophoresis and electroporation. For delivering iontophoresis pulses, all of the SS electrode wires in the first embodiment catheter or all the paired copper electrodes in the second embodiment PCB catheter are switched at the power supply to the same electrical polarity. The polarity is chosen according to the charge characteristic of the drug molecule to be delivered. A second "plate" electrode of opposite polarity is placed on the patient's skin or other body region to provide the potential or current flow required to iontophorese the drug or agent into the target tissue. Alternatively, the tip of the guide wire emerging from the distal end of the catheter may be used as the second electrode.

For electroporation of the tissue using the second embodiment, the electrodes of each pair on the PCB strips are separately energized to opposite polarities so that a field is generated across the electrode gaps.

In certain situations, a preferable approach is for electroporation to be applied to permeabilize the cells after pre-iontophoresis of the treatment agent into the tissues. Preferably, the catheter is able to perform the two procedures sequentially without repositioning of the catheter. Even more preferably, the catheter is designed to maintain a high concentration of drug in the tissue extracellular spaces (e.g. by iontophoresis) such that the subsequent creation of transient pores in cell surface membranes by electroporation pulses results in greatly improved intracellular penetration of the treatment agent.

The design of the catheters of the present invention may vary depending on the treatment agent to be delivered and the place into which the agent is to be delivered. However, since procedural simplicity and device familiarity are important considerations,

the catheters preferably resemble, in profile, a conventional over the wire balloon angioplasty catheter, but without the balloon. These catheters would be capable of passing smoothly through a conventional introducer, which would usually be shaped at the distal end according to the target vessel anatomy. During insertion into the patient, the catheter can be housed in a sheath to protect the anti-angiogenic drug depot (i.e. the region of hydrogel coating) until the treatment site is reached. When correctly positioned, the catheter can be pushed out of the protective sheath and the electrode array expanded for close juxtaposition to the tissue treatment zone. Similarly for ease of withdrawal of the catheter device from the body, the relaxed electrode network can be re-used in the sheath.

Alternative embodiments for the electrodes are described briefly. In a first embodiment, which is for iontophoresis only, the electrodes preferably comprise stainless steel wire, having polyester monofilament strands intercalated between to form an expandable tubular braid held by ferrules around a segment of a support catheter.

In a second embodiment, the electrode array is preferably a slotted polyimide/copper printed circuit board (PCB) sheet which is formed into a cylinder around a catheter body and held by ferrules at each end. The parallel slots produce a series of PCB strips which expand into a "Chinese lantern" configuration when the ferrules are moved towards each other. The outer surface of each strip then has paired electrodes of opposite polarities etched into the copper coating. A thin layer of gold preferably covers the whole PCB surface to prevent oxidation.

Preferably, the catheter has an internal lumen in the support catheter to take a guide wire for the maneuverability, torque control and other desirable properties for the catheter. Additionally, there may be one or more smaller internal lumens for wire leads to pass through the catheter body to energize electrodes mounted on the catheter near the distal tip. These wire leads may be energized from a power supply unit sited outside the body. In both embodiments, the lumen leads connect to the electrodes within the distal fixed ferrule.

The present invention allows for the electrical enhancement of drug delivery within any bodily compartment or cavity, for example, a coronary, renal or carotid artery. The drug delivery may be carried out during an angioplasty procedure or perhaps preparatory to or during implantation of a stent. The present catheters set forth may also be substituted for a balloon catheter after the sequence of balloon dilatation has been completed and the balloon withdrawn or after deployment of a stent. However, whereas a stent of conductive material may well enhance drug delivery when the catheters are used in the iontophoresis mode, such a stent may interfere with the field diagram of the paired electrodes when used in the electroporation mode. In this event, electrically enhanced drug delivery should be carried out before stent deployment.

In some circumstances it may be appropriate to institute a drug delivery therapy before balloon dilatation or before stent implantation is performed. In this situation, the present catheter would be withdrawn and the angioplasty catheter or the balloon mounted stent would be passed into the artery through the same introducer.

For some treatment protocols, simple iontophoretic enhancement of local drug delivery may suffice. Providing high doses of a drug within target cells in this way may avoid the need for sustaining systemic concentrations of levels where side effects become a serious problem.

For localized drug delivery to tissues *in vivo*, the combined use of both iontophoresis and electroporation procedures in sequence may be performed. For such a sequential process, an anti-angiogenic drug would be delivered from the catheter into the tissue by pre-iontophoresis to give a high concentration of the treatment agent in the extracellular space. The iontophoresis pulsing would be followed immediately by electroporation pulsing to permeabilize the membranes of cells within the tissue. A rapid gradient-driven diffusion of the treatment agent into the transiently permeabilized cells would facilitate targeting of the agent to intracellular elements and metabolic pathways at a concentration that is therapeutically effective. One of the catheter embodiments discussed herein is capable of performing these sequential processes without repositioning of the catheter by simple switching at the power supply outside the body. In a further variation in this catheter design, separate collector plates for the different PCB strips can be designed into the PCB circuitry. These can be connected to separate wires in the ferrule extending through lumens in the catheter body to the power supply unit. By simple switching, the electrode pairs in the PCB strips can be selectively energized in either the iontophoresis or electroporation mode. This facility allows for an even more localized treatment of a region of tissue (for example, in an artery) where a lesion site is eccentrically located in the lumen, without applying electrical energy to nearby normal or non-target tissue.

As used herein, the term "iontophoresis" means the migration of ionizable molecules through a medium driven by an applied low level electrical potential. This electrically mediated movement of molecules into tissues is superimposed upon concentration gradient dependent diffusion processes. If the medium or tissue through which the molecules travel also carries a charge, some electro-osmotic flow occurs. However, generally, the rate of migration of molecules with a net negative charge towards the positive electrode and *vice versa* is determined by the net charge on the moving molecules and the applied electrical potential. The driving force may also be considered as electrostatic repulsion. Iontophoresis usually requires relatively low constant DC current in the range of from about 2-5 mA. In a well established application of iontophoresis, that of enhancing drug delivery through the skin (transdermal

iontophoresis), one electrode is positioned over the treatment area and the second electrode is located at a remote site, usually somewhere else on the skin. With the present invention the return electrode may be similarly positioned on the skin. Alternatively the tip of the guide wire emerging from the distal end of the support catheter may serve as the return electrode. The applied potential for iontophoresis will depend upon number of factors, such as the electrode configuration and position on the tissue, the nature and charge characteristics of the molecules to be delivered, and the presence of other ionic species within the polymer matrix and in the tissue extracellular compartments.

As used herein, the term "electroporation" means the temporary creation of holes or pores in the surface of a cell membrane by an applied electrical potential and through which therapeutic agents may pass into the cell. Electroporation is now widely used in biology, particularly for transfection studies, where plasmids, DNA fragments and other genetic material are introduced into living cells. During electroporation pulsing, molecules which are not normally membrane permeant are able to pass from the extracellular environment into the cells during the period of induced reversible membrane permeabilization. The permeabilized state is caused by the generation of an electrical field in the cell suspension or tissue of sufficient field strength to perturb the cell surface membrane's proteolipid structure. This perturbation (sometimes referred to as dielectric breakdown) is believed to be due to both a constituent charge separation and the effect of viscoelastic compression forces within the membrane and it's sub-adjacent cytoskeletal structures. The result is a localized membrane thinning. At a critical external field strength, pores or small domains of increased permeability are formed in the membrane proteolipid bi-layer.

During this short period of permeabilization, external agents can rapidly transfer across the surface membrane via these pores and become encapsulated within the cell's cytosol compartment when the membrane reseals. With appropriate electrical parameters for the poration (field strength, pulse width, number of pulses etc), resealing of the membrane begins almost immediately after the pulsing, and little, if any, leakage of cytosol constituents occurs. Providing that a threshold field strength has not been exceeded, the surface membrane can reorganize with a full restoration of it's former structural integrity, receptor status and other functional properties. The resealing rate is temperature sensitive (with an optimum temperature around 37 °C). The temperature depends on the phase transition temperature of lipids in the membrane bi-layer and the capacity of proteins, and other integral membrane constituents, to diffuse laterally within the bi-layer. Too high a field strength can cause membrane breakdown beyond it's capacity to reseal the electropores.

Electrical fields for poration are commonly generated by capacitor discharge power units using pulses of very short (micro to millisecond) time course. Square wave and radio frequency pulses have also been used for cell electroporation. Of the commercially available power supplies suitable for electroporation, the ECM Voltage Generator ECM 600, available from BTX Inc of San Diego California, generates an exponential decay pulse which can be adjusted through resistor selection and different capacitor ranges to give pulse lengths in the range microseconds to milliseconds suitable for electroporating living cells. With narrow electrode gap widths such as the 0.1 or 0.2 mm gaps suggested here for the PCB electrode pairs, appropriate field strengths for tissue electroporation are possible (Kvolts/cm) using low, physiologically acceptable input voltages.

To date, most of the literature reports on electroporation have been concerned with cells in suspension and there is little if any background on cells resident in tissues. It has been reported that cells in monolayer culture, simulating an attached epithelium, require lower field strengths for successful poration (as indexed by higher transfection rates) than the same cells in free suspension. Moreover, cells in tissues which are in electrical contact or which can communicate by molecular conversation with neighbor cells through junctions can generally be electroporated at lower field strengths than the same cells in which are in a single cell suspension.

Animal cells in suspension can be electroporated with field strengths in the range 0.5 to 7.0 Kvolts/cm and the critical field strength for successful permeabilisation with resealing varies inversely with cell size, at least for cells which are approximately spherical in shape. It is this inverse relationship that allows the application of a field strength sufficient to porate a cell's surface membrane without disruption of the boundary membranes of important intracellular organelles and other structures.

Although the present inventions may have wider application in locally delivering drugs to many different tubular tissues of the body, particular applications preferred are in percutaneous transluminal coronary angioplasty ("PTCA"), after stent implantation and during arterial and venous graft implantation.

PTCA is regarded as a preferred lower risk alternative to bypass surgery when one or more arteries of the heart have become constricted due to disease. Inadequate arterial blood flow compromises the oxygenation of nearby heart tissue and if untreated, irreversible myocardial dysfunction and necrosis can result.

Two preferred catheter embodiments are set forth below. The first embodiment is preferably used only for iontophoretically enhanced drug delivery. The second embodiment may be used for enhancing the local delivery of drugs by either iontophoresis only, electroporation only or both procedures applied sequentially.

As shown in Figure 1, the catheter **10** has a proximal end **12** and a distal end **14**. At the proximal end **12** of the support catheter **10**, in a position normally occupied by a balloon, is a short (~ 4-6 cm) expandable tubular braided sleeve **20**, comprising wires or electrodes **24** mounted around and parallel to the catheter body **16**. The sleeve **20** may also comprise polyester monofilaments **28** (preferably of the same thickness as the wire electrodes) intercalated between the electrodes **24** during the braiding process. Alternatively, while the electrodes **24** may be made from a metal, such as copper, gold, platinum, stainless steel, or silver, the electrodes may also be made of carbon fiber filaments.

As shown in Figure 1, the electrodes **24**, when relaxed, lie close to the body of the support catheter thereby allowing the catheter to be passed into a blood vessel or other tubular compartment of the body using an introducer. When located in an artery, the electrodes **24** may then be mechanically expanded, as shown in Figure 2. In the middle region of the expanded electrodes **24**, a majority of the individual electrodes **24** are closely juxtaposed to the tissue to be treated. This middle region of the electrodes **24** may be coated with a visco-elastic polymer matrix incorporating the drug or other therapeutic agent to be locally delivered into the tissue. Although the electrode array is radio opaque, positioning of the catheter **10** in the treatment zone may be further assisted by strategically placed radio-opaque markers located on the support catheter body.

In the first embodiment suitable for iontophoresis, the electrodes **24** preferably comprise stainless steel wire. The electrodes are preferably integral to a short length (~ 2-6 cm) of the braided polyester filament sleeve **20** which fits closely over the support catheter **10** near the distal end **14**. In one variation, the electrodes **24** comprise 316 graded stainless steel wire (or similar conductive metal or carbon fiber). The wire for the electrodes **24** is preferably able to be bent without kinking. Preferably, the electrodes **24** should have a thickness of from about 0.10 to about 0.20 mm. More preferably, the electrodes **24** should have a thickness of from about 0.12 to about 0.14 mm. The thickness is determined by the outside diameter of the support catheter **10** and the number and spacing of the electrodes **24** around the support catheter **10** which are required for a particular treatment strategy. The electrode wires can be intercalated between polyester monofilaments **28** having approximately the same diameter as the electrodes **24**. The polyester monofilaments **28** provide structural support to the network during spinning of the braided sleeve **20** and also when the braided sleeve **20** is expanded. The polyester monofilaments **28** also assist in allowing the network to be compressed such that it fits closely to the catheter body for ease in passing the device down an introducer, along a vessel or in withdrawal of the catheter into the sleeve and out of the body after use.

The electrodes **24** and the polyester monofilament fiber **28** are preferably formed by spinning. During the spinning of the braid, the electrode wire **24** and polyester fiber **28** are fed into the machine from different spools and become configured into a parallel array around the circumference of the tubular sleeve **20**. The sleeve **20** is spun to an internal diameter that fits closely over the support catheter **10** and is then cut to a length determined by the degree of expansion of the sleeve required for a particular delivery application. In practice, a length of 3-5 cm and a maximum sleeve expansion of from about 120 to about 150 percent, with respect to the initial resting diameter, will be suitable for most tissue applications. However, the amount of expansion may vary with the different tissue structures to be treated. The number of spools used during spinning determines the openness of the weave when the sleeve is expanded.

The electrodes **24** and non-conductive polyester monofilaments **28** are held tightly at each end of the sleeve **20** using ferrule rings **34, 36**. The ferrule rings **34, 36** may be made from any material such as metal or plastic. The ferrule **34** at the distal end **14** of the electrode sleeve **20** is usually firmly fixed to the support catheter **10**. However, the ferrule **36** at the proximal end **12** is able to selectively slide axially back and forth along the support catheter body **10**. Movement of this proximal end **12** ferrule **36**, with respect to the support catheter **10**, controls the degree of expansion of the electrode network. The electrodes **24** are usually bonded to the ferrule ring **34** in the distal end **14** such that good electrical continuity exists. As shown in Figure 3, The wire lead **50** emerging from the internal lumen **40** of the support catheter **10** near the distal end **14** ferrule **34** is bonded thereto and serves to connect the electrodes **24** in the sleeve to a power supply unit (not shown). The proximal end **12** ferrule **36**, which is free to move on the catheter body, is preferably similar in construction to the distal ferrule **14** with the electrode wires **24** and polyester monofilaments **28** bonded within it. However, there is no connection of the electrodes **24** to the power supply within the proximal ferrule **12**. The outer coating of both ferrules **34, 36** is preferably made from a non-conductive material. The remainder of the catheter interior **48** is used as a guide wire lumen.

The fixed distal end ferrule **14** may include an inner insulating ring **42** and/or an insulating coat **44**. These insulating layers may be of any known insulating material, such as plastics, polyvinyl-polyethylene composites. Examples of materials useful in the present invention include plastics such as TEFLON®. Additionally, a metal ring **46** may be included for attachment to the electrode wires.

In operation, the catheter **10** is placed near the target cells. When the catheter **10** is in position for treatment with the electrode network adjacent to the treatment area, the ferrule ring **36** is manipulated to expand (or balloon out) the electrode sleeve **20** into an open mesh network. The degree of expansion depends on the bore of the artery, but it is controlled so that the electrodes **24** press firmly on the vessel wall tissue. To effect the

network expansion, the proximal end of the free sliding ferrule **36** is held stationary using a close fitting outer guide catheter tube **38**. The outer catheter tube is sleeved over the support catheter body **10** from the proximal end **12** until it abuts the end of the proximal end **12** ferrule **36**. While holding the outer catheter tube (not shown) in position against the ferrule **36**, the support catheter **10** is then slowly drawn back towards the proximal end **12** fixed ferrule **36**. This movement forces the electrodes **24** to expand outward from the catheter body **10** so that the electrodes **24** can press firmly against the tissue area to be treated, such as the luminal face of an artery. This reciprocal manipulation of the catheter **10** and guide sleeve can be pre-calibrated for different degrees of network expansion appropriate to the vessel bore in the area to be treated. If needed, the expansion/relaxation sequence may be mechanized using a motorized ratchet device which controls the movement of the support catheter **10**.

One of the novel and important features of the present invention is that since the polymer coating is present only in the middle region of the electrodes **24**, after expansion of the network, the polymer matrix is positioned on the vessel wall or tissue. There are adequate open interstices in the remainder of the network closer to the support catheter body **10** for blood to flow through the artery during electrical pulsing and drug delivery. This is greatly advantageous over catheters having electrodes positioned within or on the surface of an occlusive balloon in terms of reducing ischaemic risk. Although a perfusion lumen is generally incorporated in the catheter body of iontophoretic balloon catheters, these perfusion lumens bypass the occluded region and only prevent ischaemia downstream of the occluding balloon. Such catheters rarely provide an adequate blood flow rate for drug delivery treatment schedules extending beyond about one minute. The design of the present invention obviates the need for a perfusion lumen.

In using the present device for iontophoretically enhanced anti-angiogenic drug delivery, a separate plate electrode of opposite polarity to the catheter electrodes is used in order to generate the potential gradient across the artery or other body tissue. This plate electrode is positioned elsewhere on the patient's body (usually the skin) and may be attached using any known means, such as ECG conductive jelly.

The polarity direction for the network and plate electrodes is selected according to the charge characteristics of the treatment agent to be delivered. Positively charged agents will iontophoretically migrate towards the negatively charged electrode and vice versa.

A second embodiment of the present invention uses a printed circuit board for the electrodes **24**. This embodiment allows for anti-angiogenic drug delivery using only iontophoretic enhancement, drug delivery using only electroporation, or a combined strategy involving the initial delivery of the drug into the artery wall using

pre-iontophoresis, followed by electroporation of the tissue cells to facilitate cellular entry of the drug for targeting intracellular structures or pathways.

In this second embodiment, the catheter body **10** is essentially the same as shown in Figure 1. However, the electrode array **24** is of a different construction and consists of a series of very narrow tapes **70** formed by making a series of parallel slots **90** cut in the middle region of a rectangular flexible printed circuit board. The board can be rolled into a cylinder and affixed to the catheter body **10** within the two ferrules. The distal ferrule **14** is fixed to the catheter body **10** and the proximal ferrule **12** is free to move axially. The slots **90** do not extend the full length of the rectangle. An uncut connected region **92** is left at each end for fitting into ferrules. The electrode array **24** is constructed by etching out a flat metal sheet, such as copper, gold platinum, silver or titanium, which is attached to a base material. Preferably, printed circuit board comprises a polyimide/copper sandwich. The base and metal sheet sandwich is rectangular with the short sides being of a length equal to the circumference of the catheter **10** such that when the sheet is rolled into a cylinder to fit into the ferrules **34** on the support catheter **10**, there will be no overlap. The length of the longer side of the rectangle will be determined by the amount of electrode expansion required for a particular application. The paired electrode tracks are etched into this plate by a conventional procedure familiar to those skilled in the art of PCB manufacture. Preferably, the entire PCB is coated with a thin layer of gold on its upper copper surface.

As shown in Figure 4, the cross-sectional area of the catheter includes an internal lumen **74** for the positive lead, an internal lumen **76** for the negative lead, a lumen for the guide wire **78** and lead wires **80**, **82** for the respective positive and negative leads. Positive and negative collecting plates **84** and **86** are bonded directly to the appropriate polarity wire emerging from the catheter lumen. Finally, as discussed above, insulating layers **88**, **89** may be included.

In a preferred design arrangement, the collecting plates are oriented such that, when the PCB plate is rolled into a cylinder, the collecting plates are located at opposite sides of the catheter.

The commercial procedure for making such conductive tracks in the copper is familiar technology to those skilled in the art of integrated circuitry manufacture, minicomputer motherboard production and other forms of micro circuitry instrumentation. The electrodes may be coated with a thin layer of gold after production if desired. This coating is able to prevent oxidation processes occurring on the electrodes which would affect their efficiency.

In one of these procedures, a series of slots **90** are made right through the PCB giving a row of separate tapes. Each series of slots **90** carries a pair of electrodes **24** of opposite polarities. These slots **90** allow the electrode array to expand outwards to press

against the vessel wall when the ferrules **34** on the catheter body **10** are brought closer together, as described above. The slots **90** preferably do not extend the length of the PCB plate, but instead a narrow strip **92** is left unslotted at each end joining the individual tapes together. In the joined region at one end of the PCB, tracks are etched to connect one of each pair of electrodes to a collecting plate in the corner of the PCB. The remaining electrodes **24** of each pair are similarly tracked to a common collecting plate situated halfway along the end region. This separation of the two collecting plates by a distance roughly equal to half the eventual tubular circumference creates good insulation and also allows the lumen lead wires to emerge from the catheter body on opposite sides. Each tape carries a pair of electrodes **24** of opposite polarities with a narrow electrode gap space between them.

Figure 5(a) shows the PCB with the paired electrode tracks and the collecting plates connected to electrodes **24** of the same polarity. Figure 5(b) shows the PCB with only the slots **90** drawn. Figure 5(c) shows all the features in detail including the slots **90** and the paired electrode tracks.

In a preferred embodiment, there are 8 parallel pairs of electrodes **24**, with each electrode being from about 0.15 to about 0.3 mm wide. More preferably, the electrodes are about 0.2 mm in width with a gap width of 0.2 mm. Preferably, the electrodes **24** extend the full depth of the metal sheet **70**, preferably of copper, down to the base material **72**, preferably a polyimide. The electrode gaps between each pair would be about the width of the electrodes, also about 0.2 mm. However, the distance between the electrodes **24** and the slots **90** and the distance between the electrodes **24** and the edge of the PCB plate is preferably about 0.5 mm. Smaller distances (from about 0.125 to about 0.2 mm) are possible for PCB cylinders suitable for mounting on catheters of outer dimensions as low as 2 mm.

Depending on the size and thickness of the PCB electrode strips, an additional support layer may be needed in order to ensure that, when used, the electrodes **24** expand outward and contact the vessel walls. This additional support may be accomplished by providing an additional layer of polyimide specifically to the middle region on the underside of the PCB strips. Alternatively, when forming the electrode tracks, it may be possible to control the etching process to selectively etch certain portions of the PCB plate such that the electrodes on the strips have greater structural strength in the bonded regions.

At each end of the PCB plate, the joining strip is extended on one side to give a tab **94** which facilitates the fixing of the tubular formed electrode **24** array into the ferrules **34, 36** on the catheter body **10**. These ferrules are preferably short plastic (non-conductive) cylinders into which each end of the tubular electrode **24** array is bonded. In the fixed ferrule at the distal end **14**, an electrical connection is made between the

electrode collecting plates and the appropriate lumen leads (not shown) emerging from the catheter **10** under the fixed ferrule. By tracking the electrodes **24** of different polarities to separate collecting plates at the fixed ferrule end of the electrode **24** array, no lumen lead connection is required in the free moving ferrule **36** at the proximal end **12** of the electrode array. This ferrule is bonded only to the joining strip of the PCB and not to the catheter body.

In Figure 6, the preferred embodiment of the PCB electrode **100** is provided. This embodiment includes a flexible polyimide base layer **102**, a copper electrode layer **106** and a glue or other adhesive layer **104** for binding the polyimide layer **102** to the copper electrode layer **106**. Additionally, the PCB electrode **100** includes a gold coating **108** on the copper electrode layer **106**. Preferably, the polyimide base layer **102** is about 50 microns in thickness, the glue or adhesive layer **104** is about 25 microns in thickness, the copper electrode layer **106** is about 17.5 microns in thickness and the gold coating **108** is about 2 microns in thickness. Also, in the preferred embodiment, the PCB plate carrying 8 pairs of electrodes has a short side dimension of 0.592 inches (15.037 mm). Rolled into cylindrical form along it's long side results in a tubular electrode array that fits closely to a catheter body having an outer diameter of 3.9 mm. However, while these are the preferred dimensions, PCB plates are commonly made that are sufficiently flexible such that they may be rolled into a cylinder having a radius as small as 10 times their thickness. One skilled in the art will recognize that by reducing the thickness of the polyimide/copper PCB plate, by reducing the electrode spacing and slot edge to electrode track spaces, and/or by varying the number of paired electrode tracks, it would be possible to fabricate a PBC electrode array that is capable of fitting onto a 2-3 mm outer diameter catheter body, or even smaller.

The length of the catheter along the long side may be selected as needed. However, in a preferred embodiment, the catheter has a length of 1.571 inches (39.903 mm). However, the catheter length may be varied to allow for different expansion diameters also to allow for short or long segments of the target tissue to be treated. In one variation of this embodiment, the distal end fixed ferrule may include metal plates or studs in the ferrule which are connected to the appropriate lumen leads. The electrode would be a preformed cylindrical cassette-type electrode with an integral proximal end ferrule. Each cassette electrode would have the same diameter to fit a particular catheter body and also having at one end connectors which connect with the metal plates or studs in the fixed ferrule. Then, depending on the treatment parameters required, different cassette electrodes could then be used by sliding them onto the catheter and "plugging in" the proper cassette electrode into the distal end fixed ferrule. These cassettes could be preloaded with polymers containing different drugs.

When used for electroporation, the catheter may be connected to a suitable pulse generator. The generator sends pulses to the tissue across narrow electrode gaps. These pulses are preferably of a field strength (volts/cm.) in the range used for cell electroporation and generated at low and physiologically acceptable peak input voltages. For example a peak input voltage of, for example, 30 volts with electrode gap widths of 0.2 mm would give a field strength of 1.5 kV/cm. (i.e. 50 x 30 volts). A reduction in electrode gap width or an increase in input voltage would give a corresponding increase in field strength.

Additionally, the lumen leads may be modified such that power is only delivered to a few of the electrodes. In this manner, only the portion of the vessel walls that requires treatment would be treated. This may be accomplished by taking the leads for selected electrode pairs right through the catheter lumens to the power supply where they can be switched "on" or "off" according to need. Polarity selection in the ferrule could be achieved by an electrode of one polarity passing through the polyimide base material through "vias" or holes to a common terminal on the underside of the PCB. This is a common configuration in printed circuit boards. In this way, treatment can be restricted to a segment of the luminal circumference.

The electrodes in the device may also be all switched to single polarity for use with an external plate electrode for iontophoresis or switched to electrode pairs of opposite polarity for electroporation. In the latter procedure, an external plate electrode is not required and this is simply disconnected at the power supply.

The catheter may be used, as discussed above, in a combined iontophoresis/electroporation process, such as for an angioplasty procedure. First, after balloon dilatation, a period of continuous or pulsed iontophoresis would first be applied to enhance drug migration out of the polymer coating and into the artery wall tissue to raise the drug concentration to a sufficiently high level within the tissue extracellular spaces. Since blood is still able to flow through the artery during electrical pulsing, iontophoretic delivery can be extended for much longer periods than is possible with delivery devices using fully occlusive balloons. After iontophoretic delivery, and without removing or repositioning the catheter, the electrodes on the catheter would be switched from their single polarity to the paired electrode mode in each PCB strip. The vessel wall would then be subjected to a series of high field strength, very short time electroporation pulses to transiently electroporate the surface membranes of cells in the artery wall tissue. The drug in the extracellular spaces of the tissue is then able to rapidly diffuse down a concentration gradient through the open cell membrane pores, enter the cell's cytosol compartments for targeting to intracellular structures such as the nucleus, cytoskeletal elements and metabolic or signal transduction pathways. The porated cell membranes would subsequently reseal with full restoration of cell integrity.

Finally for withdrawal of the device after treatment, the guide (sleeve) catheter used for electrode network expansion would be returned to its original placement and the catheter would be removed.

The anti-angiogenic treatment agent may be delivered through the catheter using several different embodiments. In one embodiment, which may be used with any of the catheter embodiments set forth, the treatment agent is incorporated within a polymer matrix, and this matrix is applied as a coating to the middle region of the electrode array. The treatment agent is may then be iontophoretically driven out of this polymer matrix into the adjacent tissue. The polymer matrix preferably has a good drug holding capacity and is sufficiently pliant to be compressed against the tissue when the electrode network is expanded.

In a second embodiment, the polymer matrix containing the anti-angiogenic drug is instead molded into a short tubular expandable visco-elastic sleeve which fits over the middle region of the electrode array in its relaxed position. When the electrode network is expanded, the polymer sleeve expands as well until it is pressed against the tissue to be treated. In a third embodiment, the drug holding polymer matrix may be prelaid or prepolymerized as a "lawn" or "paving" on the surface of the tissue to which the electrodes are subsequently juxtaposed for iontophoretically moving the treatment agent out of the polymer and into the adjacent tissue.

With respect to the polymer composition, the term "polymer matrix" as used herein includes synthetic hydrogel polymers with pores or interstices of different sizes and capacities introduced during manufacture, and a variety of synthetic elastomers and naturally occurring polymeric materials known to those skilled in the art. The anti-angiogenic agent can be incorporated in the matrix either during polymer production or added after coating or molding of the polymer into the desired shape. Additionally, many of a number of different polymeric materials and methods of fabrication may be used to form the polymer matrices used in the present invention. Examples of suitable polymer materials or combinations include, but are not limited to, biocompatible and/or biodegradable polymers such as poly(lactides), polyglycolides, polyanhydrides, polyorthoesters, polyactals, polydihydropyrans, polycyanoacrylates and copolymers of these and polyethylene glycol. These can take the form of co-polymer hydrogels or cross-linked polymer networks into which drugs for electrically enhanced local delivery can be incorporated either during polymerization or, in the case of certain hydrogels, loaded subsequently. Preferable matrices would be tailored according to the molecular characteristics of the agent to restrict its loss by free diffusion outwards but allow full iontophoretic migration outwards when a potential is applied across the polymer and adjacent tissue.

In another embodiment, hollow microspheres may be used to deliver the anti-angiogenic agent. The drug is located within the hollow portion of the microsphere. The drug-laden microspheres may then be injected near the tissue to be treated and activated by the catheter thereby driving the drug from the microspheres into the tissue. A plurality of different drugs may be delivered by using multiple types of microspheres and varying frequencies to deliver the different drugs as needed. Microspheres useful in the present invention include those sold under the name biSphere™ available from POINT Biomedical (San Carlos, CA). These microspheres are 3-6 μm in diameter, feature double-walled construction and are fully biodegradable.

Additionally, normal anti-angiogenic drug delivery means may be used in the invention as well, such as free fluid form, including combinations of different angiogenesis inhibitors and other therapeutic agents. However, use of polymer matrices has certain advantages over free fluid delivery. Delivery of an agent which has been incorporated into a polymer matrix does not require additional lumens in the support catheter to convey the free fluid drug solution into and out of the treatment site. Additionally, the polymer matrices eliminate the risk of downstream leakage of drug solution due to defective balloon sealing of vessel segments, thereby avoiding the risk of exposure of non-target tissue to high concentrations of the drug. Also, since extra liquid drug delivery lumens are not required, the catheter profile is narrower which improves its maneuverability in the body and reduces production costs.

## CLAIMS

We claim:

1. A method of inhibiting injury to vascular tissue, comprising locally administering to the vascular tissue an angiogenesis inhibiting amount of an anti-angiogenic agent, thereby inhibiting injury to the vascular tissue.

2. The method of Claim 1, wherein the vascular injury is due to atherosclerosis, cardiac transplant vasculopathy, coronary restenosis following coronary intervention, balloon angioplasty, stent placement, rotablator, carotid endarterectomy, dialysis graft stenosis, graft anastomosis neointima, unstable angina, acute myocardial infarction, stroke, benign hypertrophy, or benign prostatic hypertrophy.

3. The method of Claim 1, wherein the vascular injury is due to atherosclerosis or restenosis.

4. The method of Claim 1, wherein the anti-angiogenic agent is selected from the group consisting of AGM-1470 (TNP-470); antibody to vascular endothelial growth factor or fibroblast growth factor; batimastat (BB-94), marimastat; tyrosine kinase inhibitor, genistein, SU5416; integrin antagonist alphaVbeta3/5; retinoid, retinoic acid fenretinide; 11 α-epihydrocortisol, corteloxone, tetrahydrocortisone, 17 α-hydroxyprogesterone; protein kinase inhibitor, staurosporine, MDL 27032; 22-oxa-1 alpha, 25-dihydroxyvitamin D3; arachidonic acid inhibitor, indomethacin, sulindac; tetracycline, minocycline; thalidomide; estradiol, 2-methoxyestradiol; tumor necrosis factor-alpha; interferon-gamma-inducible protein 10; interleukin 1 and interleukin 12; interferon alpha, beta or gamma; Angiostatin® protein, plasminogen fragment; Endostatin™ protein, collagen fragment; proliferin-related protein; group B streptococcus toxin; CM1O1; CM; troponin I; squalamine; nitric oxide synthase inhibitor, L-NAME; thrombospondin; wortmannin; amiloride; spironolactone; ursodeoxycholic acid; bufalin; suramin; tecogalan sodium; linoleic acid; captopril; irsogladine; FR-1 18487; triterpene acid; castanospermine; leukemia inhibitory factor; lavendustin A; platelet factor-4; herbimycin A; diaminoantraquinone; taxol; aurintricarboxylic acid; DS-4152; pentosan polysulphite; radicicol; fragments of human prolactin; erbstatin; eponemycin; shark cartilage; protamine; Louisianin A, C and D; PAF antagonist WEB 2086; auranofin; ascorbic ether; sulfated polysaccharide D 4152, anti-keloid agent, and TRANILAST.

5. The method of Claim 1, wherein the anti-angiogenic agent is locally administered via a catheter.

6. The method of Claim 5, wherein the anti-angiogenic agent is incorporated into endoluminal paving of a catheter which is directed locally to the tissue.

7. The method of Claim 1, wherein the anti-angiogenic agent is incorporated into a locally administered polymer that permits local sustained release of the anti-angiogenic agent.

8. The method of Claim 1, wherein the anti-angiogenic agent is incorporated into a stent or stent coating which is placed locally on the tissue.

9. The method of Claim 1, wherein the anti-angiogenic agent is incorporated into an endovascular graft or an endovascular graft coating which is placed locally on the tissue.

10. A method of treating injured vascular tissue, comprising locally administering to the injured vascular tissue an angiogenesis inhibiting amount of an anti-angiogenic agent, thereby treating the injured vascular tissue.

11. The method of Claim 10, wherein the vascular injury is due to atherosclerosis, cardiac transplant vasculopathy, coronary restenosis following coronary intervention, balloon angioplasty, stent placement, rotablator, carotid endarterectomy, dialysis graft stenosis, graft anastomosis neointima, unstable angina, acute myocardial infarction, stroke, benign hypertrophy, or benign prostatic hypertrophy.

12. The method of Claim 10, wherein the vascular injury is due to atherosclerosis or restenosis.

13. The method of Claim 10, wherein the anti-angiogenic agent is selected from the group consisting of AGM-1470 (TNP-470); antibody to vascular endothelial growth factor or fibroblast growth factor; batimastat (BB-94), marimastat; tyrosine kinase inhibitor, genistein, SU5416; integrin antagonist alphaVbeta3/5; retinoid, retinoic acid fenretinide; 11 α-epihydrocortisol, corteloxone, tetrahydrocortisone, 17 α-hydroxyprogesterone; protein kinase inhibitor, staurosporine, MDL 27032; 22-oxa-1 alpha, 25-dihydroxyvitamin D3; arachidonic acid inhibitor, indomethacin, sulindac; tetracycline, minocycline; thalidomide; estradiol, 2-methoxyestradiol; tumor necrosis factor-alpha; interferon-gamma-inducible protein 10; interleukin 1 and interleukin 12; interferon alpha, beta or gamma; Angiostatin® protein, plasminogen fragment; Endostatin™ protein, collagen fragment; proliferin-related protein; group B streptococcus toxin; CM1O1; CM; troponin I; squalamine; nitric oxide synthase inhibitor, L-NAME; thrombospondin; wortmannin; amiloride; spironolactone; ursodeoxycholic acid; bufalin; suramin; tecogalan sodium; linoleic acid; captopril; irsogladine; FR-l 18487; triterpene acid; castanospermine; leukemia inhibitory factor; lavendustin A; platelet factor-4; herbimycin A; diaminoantraquinone; taxol; aurintricarboxylic acid; DS-4152; pentosan polysulphite; radicicol; fragments of human prolactin; erbstatin; eponemycin; shark cartilage; protamine; Louisianin A, C and D; PAF antagonist WEB 2086; auranofin; ascorbic ether; sulfated polysaccharide D 4152, anti-keloid agent, and TRANILAST.

14. The method of Claim 10, wherein the anti-angiogenic agent is locally administered via a catheter.

15. The method of Claim 14, wherein the anti-angiogenic agent is incorporated into endoluminal paving of a catheter which is directed locally to the tissue.

16. The method of Claim 10, wherein the anti-angiogenic agent is incorporated into a locally administered polymer that permits local sustained release of the anti-angiogenic agent.

17. The method of Claim 10, wherein the anti-angiogenic agent is incorporated into a stent or stent coating which is placed locally on the tissue.

18. The method of Claim 1, wherein the anti-angiogenic agent is incorporated into an endovascular graft or an endovascular graft coating which is placed locally on the tissue.

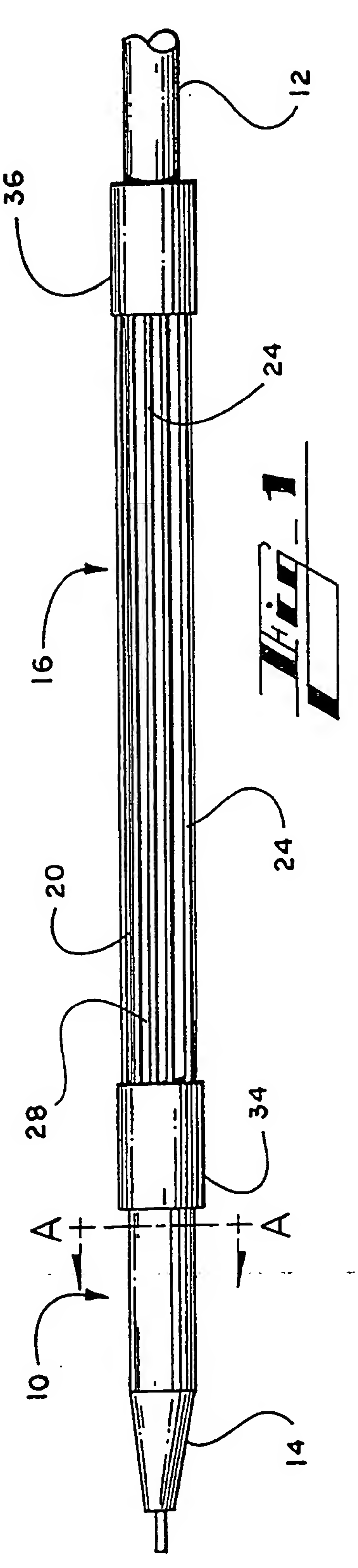


Fig_1

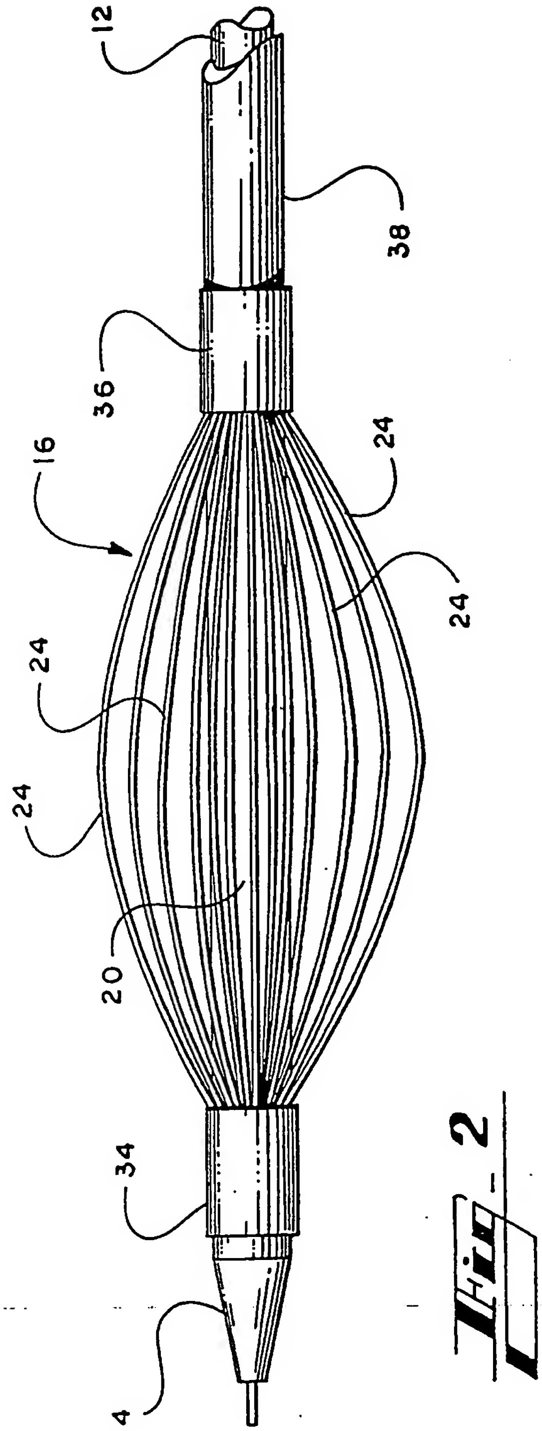


Fig_2

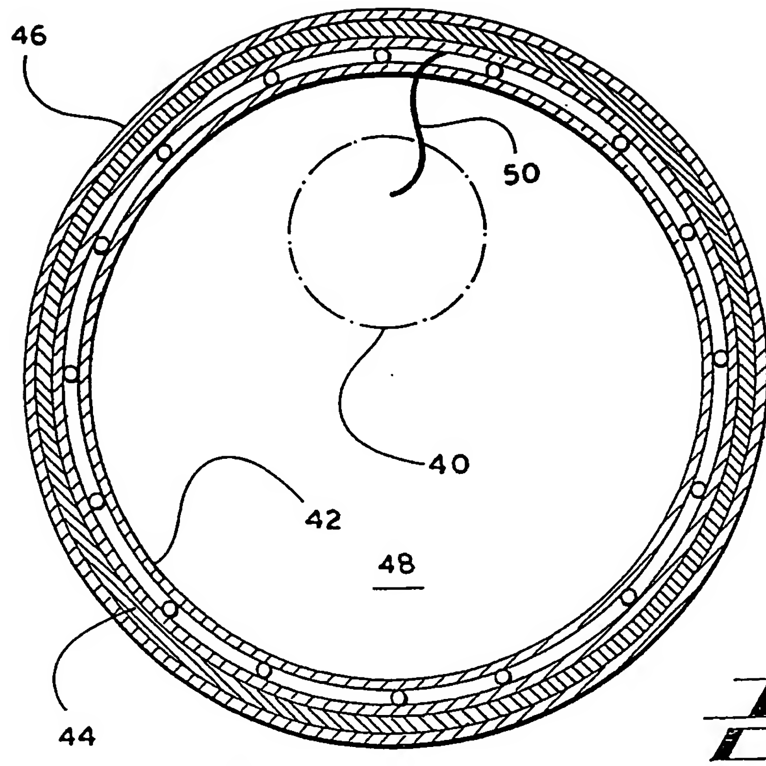


Fig. 3

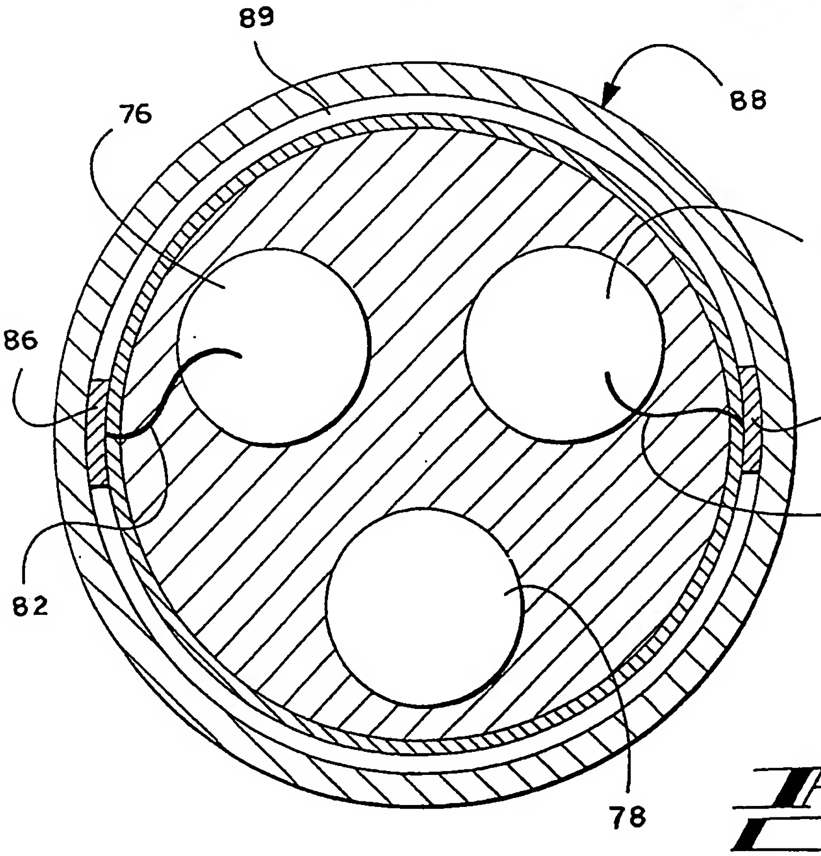


Fig. 4

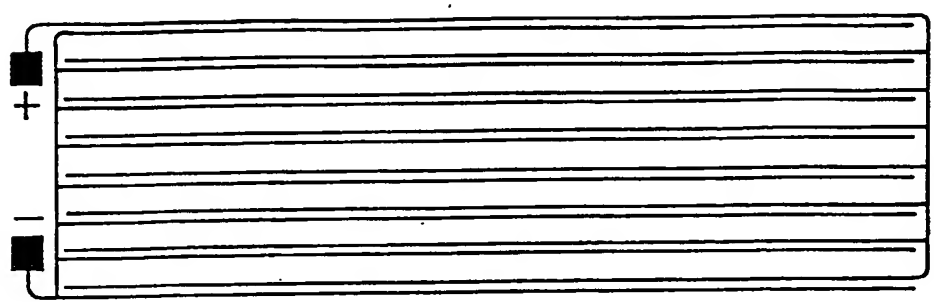


Fig_5A

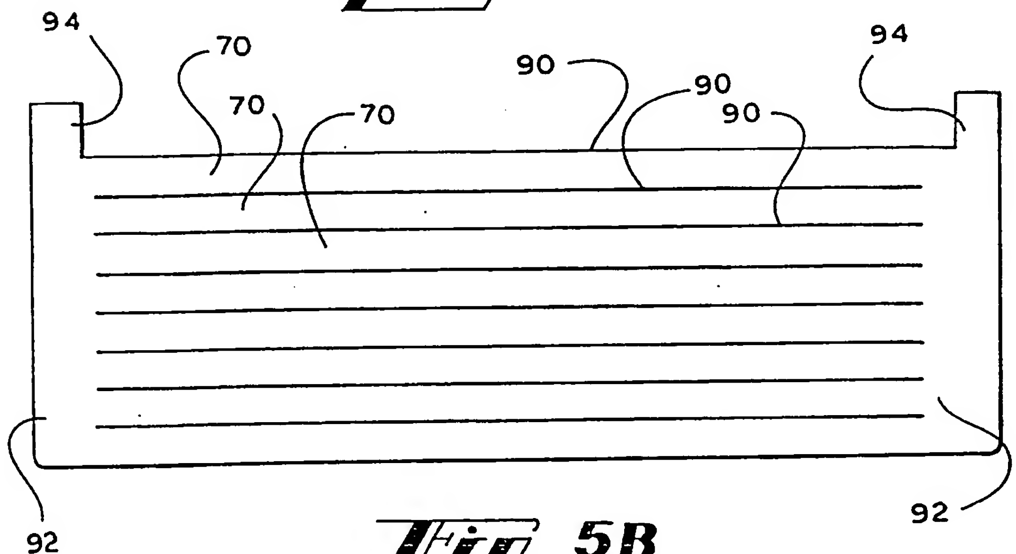


Fig_5B

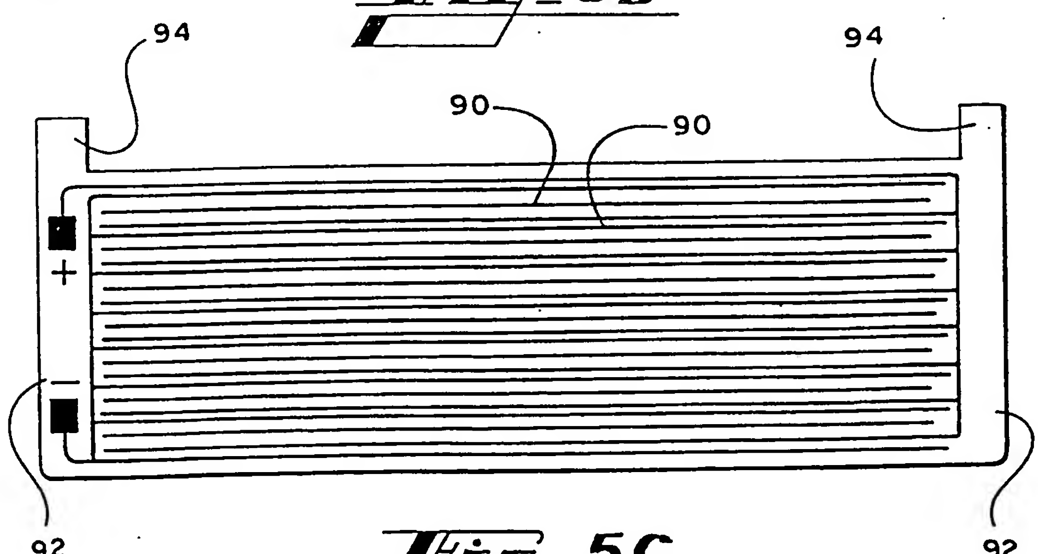


Fig_5C

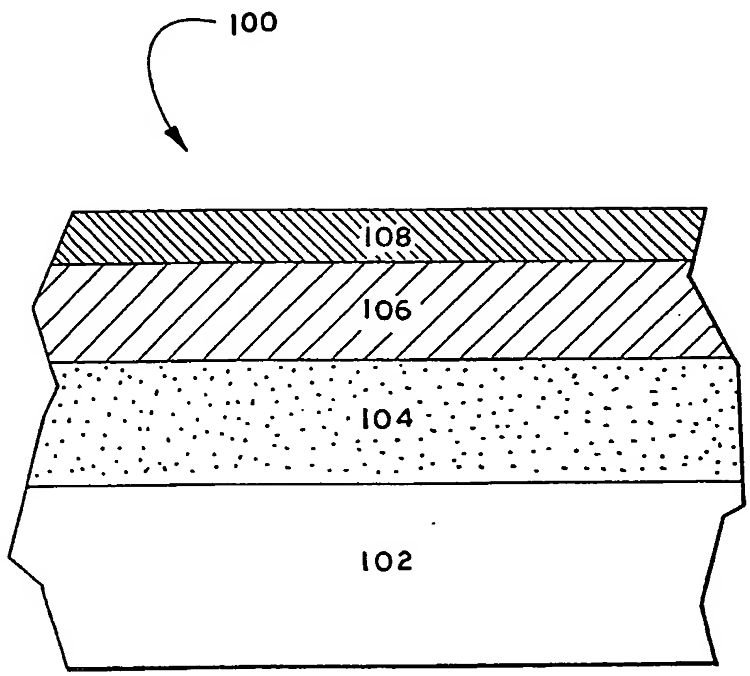


Fig. 6